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(54) **Monosaccharide containing wound healing preparation.**

(57) The present invention relates to a composition comprising at least one pharmaceutically acceptable monosaccharide containing from about 3 to 7 carbon atoms and a pharmaceutically acceptable film forming agent.

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Description

MONOSACCHARIDE CONTAINING WOUND HEALING PREPARATION

The present invention relates to methods and compositions for beneficiating wound healing. More specifically, it relates to the use of monosaccharides, especially fructose, to beneficiate wound healing processes.

During the period following development or infliction of serious physical damage to the skin, by way of for example, severe burns, wounds, pressure ulcers, and the like, the injured area is extremely unstable physiologically; following such injury or trauma, the normal physiological processes of the area in question may be severely compromised. Disruption in the normal pattern of skin growth, blood flow, and immunity may all be impaired to some extent by the trauma to the region. The physician treating such damaged tissue must therefore be able to control and eventually reverse these undesirable effects, while at the same time stimulating the processes that are necessary to achieve healing of the area.

Because of the variety of different systems which may be adversely affected by such injury, it is difficult to find a single agent which will be effective in controlling the various sources of the problems. For example, one of the most severe difficulties encountered is the immediate colonization of the wound by a variety of different types of microbial species. Common invaders of a wound site are such known pathogens as Staphylococcus aureus, as well as a number of opportunistic pathogens, such as Escherichia coli or Pseudomonas aeruginosa. Various yeasts, particularly Candida albicans, may also be found at the wound. Although a number of antimicrobial agents for topical application are known, none has proven to be without some serious disadvantage. For example, silver sulfadiazine, the current antibacterial agent of choice is effective against gram-positive bacteria and gram-negative but many resistant strains have developed in the course of its use, particularly in the genus Pseudomonas. Similarly, the commonly used Betadine (povidone-iodine), although effective against both gram-positive and gram-negative bacteria, can be quite painful to the patient upon application, kills white cells in the wound, specifically polymorphonuclear cells, lymphocytes, monocytes, and macrophages, and may cause sensitization of an area already severely traumatized. Other known antibacterial agents may be hampered in their use by low diffusibility of the composition, or a range of activity that covers relatively few types of microbes; expense, as with substances such as the various silver salts, is also a factor to be considered.

Related to the invasion by microbes of the wound site is the generally decreased circulation which is also observed in many cases. For example, in decubitus or stasis ulcers, a cessation of blood flow may develop gradually, whereas an acute cessation of flow may occur in thermo-radiation and chemical burns. In either case the decrease in the rate of blood flow means a corresponding decrease in the provision to the cells of nutrients and oxygen. Thus deprivation in turn leads to necrosis of tissue in the poorly supplied region, which will be followed by the invasion of the unwanted bacteria and fungi. In order for healing to proceed, the damaged area must not only be rid of any lingering microbial infection, but also must have a restored blood flow, which will provide sufficient nutrient and oxygen supply to support a regeneration of the wounded region. In the ideal situation, the increased blood flow should also be accompanied by the formation of healthy granulation tissue. The latter is a layer of highly vascularized tissue, containing numerous fibroblasts and collagen and ground substance, which supports the normal wound healing processes of recollagenation and reepithelialization.

Another very critical aspect of the wound healing process is the initiation of wound closure. This is generally a two-stage process, comprising contraction and epidermal migration. Contraction is the process of bulk skin movement from the edges of the wound, while migration is the separation and movement of activated epidermal cells over the surface of the wound. Because contraction itself may lead to some scarring it is preferable to be able to speed healing in a manner which will increase the process of epidermal migration. The process of migration is characterized by a stimulation of mitosis in the epidermal cells, accompanied by movement across the wound site. The extent to which epidermal migration, and thus wound closure, can be promoted will also in some cases determine whether or not additional skin grafting is required to complete the healing of the wound.

It is thus evident that a large number of different factors must be controlled and/or stimulated in order to achieve thorough regeneration of the damaged tissue. Since the processes involved, and the mechanisms controlling them, are so diverse, it has proven difficult to pinpoint a single treatment composition or method which is capable of aiding and promoting most or all of the required processes simultaneously. As noted above with respect to the various antibacterial agents available, the majority of wound healing compositions available suffer from one or another deficiencies, whether it be in complexity of application, insufficient ability to control infection, irritation caused to the patient, limited range of protective activity, or expense (See for example D. Wise (ed.) Burn Wound Coverings, Vol. I Chap, I, p. 11-22, CRC Press, 1984).

It has now been surprisingly discovered that certain monosaccharides, when used either alone or in combination with many known wound treating compositions, may have the effect of providing added protection against microbial infection, enhancing the growth of granulation tissue, promoting the vascularization of the wound site, and/or stimulating the process of epidermal migration and wound closure. When the monosaccharides are used in combination with known compositions, the effects observed on wound healing are significantly and unexpectedly improved with respect to the above features. When used alone, the monosaccharides show a remarkable and unpredicted effect on control of bacterial infection on

damaged skin. The monosaccharide fructose has proven to be most useful and successful in this regard.

Various monosaccharides have previously been known to be used for therapeutic purposes. For example, it is known to administer fructose intravenously to inhibit erythrocyte fragility during surgical extracorporeal circulation procedures (U.S. Pat. No. 4,448,771). Sorbose is also known (U.S. Pat. No. 4,390,523) to be used as a sugar substituted to inhibit acid formation by bacteria in the mouth, but it does not itself have an effect on bacterial growth. Oral administration of pure fructose is also known to control human stress response (U.S. Pat. No. 4,024,250). Bacteriostatic effects have also been attributed to irradiated glucose and fructose, but this effect is the apparent result of the peroxide compounds produced by the irradiation (Namike et al. Agr. Biol.Chem. 37(5): 989-998, 1973). The latter reference, in fact, shows normal bacterial growth in the presence of glucose and fructose. Various natural substances, such as honey or sugar (i.e., sucrose) have also been traditionally used as a type of folk-medicine for preventing infection. Thus, there has been no previous indication that monosaccharides would have any antibacterial effect either alone or in combination with other products for a topical wound healing preparation, and in fact, the monosaccharides show a more marked protective effect than disaccharides such as sucrose and lactose. As employed herein, the term wound is intended to apply to any skin or connective tissue trauma, such as thermal burns, pressure ulcers, ischemic ulcers, chemical and radiation burns, abcesses, fistulae, bone defects, malunion of fractures, vasculitis, tropical parasitic ulcers, leprosy ulcers, and acne or psoriasis lesions.

The present invention relates to a composition comprising an effective amount of at least one pharmaceutically acceptable monosaccharide containing from about 3 to 7 carbon atoms and a pharmaceutically acceptable film forming agent. In its preferred embodiment, the present invention relates to a composition comprising an effective amount of fructose and a starch hydrolysate, and preferably to a composition comprising fructose and a starch hydrolysate having a dextrose equivalent of between 13 and 17. These compositions are useful both in the treatment and healing of wounds, as well as for use as carriers for other dermatological treatment agents to be used in salve form.

The present invention also relates to the use of monosaccharides, particularly fructose, to control microbial growth in a mammalian wound.

As used in the present specification and claims, the phrase "controlling microbial growth", refers to the ability of the monosaccharide to either prevent microbial growth on an as yet uninfected wound, to prevent further growth in an already infected wound or to actually kill the microbes present in a wound. "Microbial" refers to bacterial or fungal infection.

The monosaccharides as described herein provide an unexpectedly beneficial effect when used as an addition to traditional wound healing compositions, as well as being useful alone as an antibacterial pretreatment for wounds. Particularly good effects have been observed when a monosaccharide is added in a therapeutically effective amount to various film forming agents which are routinely used as protective coverings for various types of wounds, especially burns. These agents in themselves form a simultaneous barrier to both water and microbes, and as used herein, comprise various types of dry (non-gel films, as well as biological gels (gelatin and gelatin/pectin materials), synthetic hydrogels, ionic gels and adhesives. Although monosaccharides may be effectively combined and used with any of the above materials, unusually favorable results are achieved by combining a monosaccharide, especially fructose, with a film-forming starch hydrolysate.

The therapeutic use of starch hydrolysate has been described in depth in U.S. Patent Nos. 3,812,252 and 4,414,202, the teachings of which are incorporated herein by reference. In brief, this material itself has been shown to be an exceptionally effective treatment for burns, ulcers, lesions, etc. The starch hydrolysate forms a film which ultimately adheres to underlying tissue and which is semipermeable to gas and fluid. It thus provides a covering which reduces plasma and fluid loss, while also preventing invasion by pathogenic microbes. The effects observed with use of starch hydrolysate are far superior to results seen with use of traditional wound coverings. When used in combination with a monosaccharide the effects on wound healing are tremendously enhanced, producing results which heretofore have not even been possible with the use of starch hydrolysate alone.

For example, application of a mixture of a starch hydrolysate with a monosaccharide, particularly glucose or fructose, has a remarkable effect on the process of revascularization of the wound. Within 15 minutes - 6 hours of such application, the treatment wound takes an intensely bright red color, visual evidence of the fact that new blood vessels are being formed in the region, and that normal circulation is returning to the site. Although it is part of the normal healing process that revascularization will eventually occur, the speed with which new blood vessels return to the damaged tissue when treated with starch hydrolysate and fructose is unexpectedly faster than that observed with starch hydrolysate alone. The presence of the added monosaccharide thus has a synergistic effect when combined with the starch hydrolysate, the end results being unattainable with either of the two substances used alone.

Similar surprising effects are seen in the development of granulation tissue. As noted above, the noticeable appearance of healthy granulation tissue signifies the start of the process of healing, to a large extent by virtue of a reconstruction of the connective tissue in the injured region by the numerous fibroblasts associated with granulation tissue. The use of starch hydrolysate alone does, to some degree, have a beneficial effect on promoting formation of granulation tissue; such tissue, where starch hydrolysate alone is used, has a relatively smooth appearance. On the other hand, when starch hydrolysate is used in combination with a monosaccharide, the granulation tissue takes on a significantly different appearance, being very intensely

granular, with a rough surface, indicating a greater level of activity in the tissue thus leading to a more rapid rate of healing.

Particularly remarkable, however, is the effect the added monosaccharide has on the process of wound closure. This process is extremely important in the progression of healing, since if it proceeds to completion, the necessity for skin grafts will be minimized or avoided completely. One of the major problems with many of the known film forming agents is that they rarely are capable of enhancing the wound closing process, so that, in a wound of any substantial size, a skin graft will always be required. Starch hydrolysate alone has been shown to have a dramatic effect on the process, and does significantly reduce the necessity for skin grafting. However, when combined with a monosaccharide, the results observed with respect to wound closure are truly outstanding, with much larger wounds showing complete closure in a relatively shorter period of time than has previously been known to be possible. The effect of the added monosaccharide shows itself particularly in the stimulation of epidermal mitosis and migration; this can be demonstrated both macroscopically and microscopically. Thus, the use of a composition containing both starch hydrolysate and a monosaccharide, preferably fructose, can effectively reduce or eliminate the need for a skin graft to a far greater extent than is possible with any known wound coverings.

Finally, of course, the added monosaccharide has an antibacterial effect in conjunction with the starch hydrolysate. Whereas the starch hydrolysate alone is known to have a significant ability to control the level of bacterial infection in a wound, when combined with a monosaccharide, this ability is so enhanced as to virtually completely inhibit microbial growth at the site of application. Thus, with all the superior effects observed with the application of the film-forming agent -monosaccharide combination, the present compositions provide an exceptional method of treatment for damaged or injured tissue.

The monosaccharides are also particularly useful alone as antimicrobial agents. They have been shown to be extremely effective in controlling microbial infections at the wound site, and in preventing the development of infection. These results have been observed clinically in wounds wherein bacterial and yeast growth is stopped in far less time than is normal with some of the most popular wound treatments; this has also been verified under controlled conditions in vitro. (See Example 3). These compounds are particularly desirable because they are effective in controlling growth of colonies of both gram-positive and gram-negative bacteria, as well as opportunistic yeast infections which may arise. The monosaccharides are not only microbiostatic, but also, to some extent, microbicidal. For example, exposure of bacteria commonly found in wounds to an effective amount of fructose has been shown to cause visible disruption of large numbers of bacterial cells. As noted above, the application may be made to a wound in which infection already exists, as well as to an injured area of skin which may be prone to developing infection.

The antimicrobial effects of the monosaccharides are particularly useful when utilized as a pretreatment of a wound prior to the application of proven additional methods of treatment, such as dressings, gels, films, etc., or as a postreatment therapy when other methods have failed to produced the desired results. This treatment may be accomplished in a number of ways. For example, for pretreatment of a burn patient, the area of damaged tissue may be immersed in a bath comprising a monosaccharide-containing solution, for a period of time sufficient to inhibit potential bacterial growth. The bathing solution may contain concentrations of monosaccharides from about 20 to up to about 95% but preferably the concentration will be in the range of about 20-60%.

The length of treatment by immersion will depend on the extent of the wound. For a small, fairly localized wound, the period of exposure may be up to 24 hours, depending upon the concentration of the monosaccharide in solution. It will be recognized by one skilled in the art that higher amounts of monosaccharide in the solution will exert a proportionately greater osmotic effect on the wound, and will therefore have a tendency to draw out fluids. While not a tremendous problem with smaller wounds, this effect is magnified in a patient with, for example, extensive burns requiring treatment. In such a case, it is desirable to limit the concentration of monosaccharide, or to keep the treatment period short. For example, when using high fructose corn syrup as the immersion medium for a very large wound (very convenient because of the ready availability of these products), the immersion period should be no more than about 1 or 2 hours, since the concentration of monosaccharide in the syrup is so high, approximately 95%. On the other hand, the syrup may be diluted, up to about 4 times, and the immersion time increased proportionately.

Similarly, for pretreatment of a less extensive wound, the injured area may be irrigated with the same monosaccharide solution, in the same manner as would be employed with a typical saline solution; this may also be done by an I-V drip over the damage tissue. Again, length of treatment of the wound with the method depends upon the size of the wound and the concentration of the monosaccharide. For a large wound, 1-2 hours is the maximum period recommended at one time. With a smaller wound, up to 6 hours, several times a day for a period of up to 24 hours may be permitted.

It is also possible to use the monosaccharides in dry powder form directly on the wound or burn. The powder may be simply sprinkled onto the wound, and left for a period of time consistent with the size of the wound. For example, with a smaller wound, the powder may remain for a period of up to 24 hours, with application possible being repeated 4-6 times within that period. With an extensive wound the application should generally not be prolonged beyond 1-2 hours.

In the practice of the present invention in using monosaccharide alone, the treatment solution should contain a concentration of monosaccharides of between about 20 to about 95% weight/volume and the preferred concentration is between about 20 to about 60%. To prepare the solution, the monosaccharide in

dry form may be mixed with any pharmaceutically acceptable liquid vehicle suitable for the topical treatment of wounds. The preferred diluents are distilled water, any balanced salt solution, normal saline or Ringer's solution. These and other pharmaceutically acceptable solutions will be well known to the skilled artisan; particularly preferred are balanced salt solutions which have themselves been shown to have a beneficial effect on wound healing processes (U.S. Patent No. 4,414,202). The pH of the solution should be maintained between about 5 to about 7.4; preferably about 6-7. Alternately, the solution used may be any of the currently available high fructose corn syrups, either diluted or undiluted. For use in dry form, the monosaccharide may be any chemically pure powder. Particularly useful is dried high fructose corn syrup powder, such as is produced by American Maize Company (Indiana). This product comprises a mixture of about 95% glucose and fructose, the remainder being sugars of higher molecular weight.

The film-forming composition of the present invention comprises an effective amount of at least one pharmaceutically acceptable monosaccharide containing from about 3 to 7 carbon atoms and a pharmaceutically acceptable film-forming agent.

In a preferred embodiment, the pharmaceutically acceptable monosaccharide of the present invention is a pharmaceutically acceptable aldose sugar or a pharmaceutically acceptable ketose sugar. Among the pharmaceutically acceptable aldose sugars within the contemplation of the present invention are erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose and talose. Among the pharmaceutically acceptable ketose sugars preferred for use in the composition of the present invention are erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, and sedoheptulose. Although either (D) or (L) isomers maybe employed, the (D) form is generally preferable. Although all of the above aldose and ketose sugars maybe employed as the monosaccharide component of the composition of the present invention, glucose of the aldose sugars and fructose and sorbose among the ketose sugars are particularly preferred. Overall, the ketose sugars are most particularly preferred, and of these, fructose is the most preferred monosaccharide for use in the composition of the present invention, since the proportions necessary to achieve the desired effect are smaller when fructose is used. The monosaccharide is preferably present, in an amount of between about .01 to about 50% by weight of the composition. Most preferably, the monosaccharide is present in an amount of between about 5 to about 30% of the weight of the composition. The monosaccharide component may also be a mixture of two or more monosaccharides. For example, high fructose corn syrups are available in powder form; these generally contain about a 95% combination of glucose and fructose, in approximately equal amounts. Such powders may be also combined with the starch hydrolysate, preferably in an amount of up to about 30%, in lieu of addition of a single monosaccharide.

In another preferred embodiment of this invention the pharmaceutically acceptable film-forming agents include, but are not limited to, any of starch hydrolysate, polyvinyl pyrollidone, polyvinyl alcohol, ethylene glycol, albumin, cellulose, gelatin, solubilized keratin, hydrocolloids such as alginate, karaya gum, gum arabic, gum tragacanth, agar, and locust bean gum. Of these film-forming agents, starch hydrolysate is most preferred.

Those skilled in the art are aware that starch hydrolysate is a generic term of a mixture of carbohydrates most commonly classified according to its dextrose equivalent. The starch hydrolysate of the present invention is one which has a dextrose equivalent of no more than 85, but preferably no more than 40. More preferably, the dextrose equivalent of the starch hydrolysate of the present invention is between about 5 and 40. Still more preferably, the dextrose equivalent of the starch hydrolysate is between about 7.5 and 30. Yet still more preferred is a starch hydrolysate having a dextrose equivalent in the range of between about 10 and 20. Most preferably, the starch hydrolysate of the present invention has a dextrose equivalent in the range of between about 13 and 17. Those skilled in the art are aware that starch hydrolysates having a dextrose equivalent in this latter most preferred range are more specifically maltodextrins. It will also be understood that "pharmaceutically acceptable" means purified and sterilized. Any of the known methods, including dry heat, filtration, or irradiation may be used for the sterilization, although for the monosaccharide, irradiation is not particularly recommended because of the possible effect on the molecular structure.

The action of the film-forming agent combined with monosaccharide may be further enhanced by the incorporation of small amounts of optional ingredients. The optional components generally do not constitute more than 5% of the total weight of the composition.

In another preferred embodiment, a principal additional component of the composition of the present invention is one which includes ascorbic acid or a pharmaceutically acceptable salt thereof. Those skilled in the art are aware that ascorbic acid or a pharmaceutically acceptable salt thereof promotes the formation and growth of healthy granulation tissue. Among the pharmaceutically acceptable ascorbate salts contemplated for use in this invention are sodium ascorbate, potassium ascorbate and calcium ascorbate. However, it is emphasized that the acid, ascorbic acid itself, is most preferred. When employed, the ascorbic component is preferably used in an amount of from about 0.1-5% of the total weight of the composition, and most preferably comprises about 1-3.5% of the composition.

In another preferred embodiment, the composition of the present invention includes one or more pharmaceutically acceptable metal salts selected from the group consisting of iron, calcium, copper, magnesium, selenium, silver, manganese, zinc and mixtures thereof. The incorporation of one or more of these salts in the composition of the present invention beneficiates the process of its healing. Among the preferred salts, a ferrous(iron II) containing salt is most preferred. For example, the utilization of one of ferrous sulfate, ferrous chloride or ferrous gluconate is preferred. Of these, the use of ferrous sulfate is particularly preferred.

It is emphasized that more than one of these salts may be included in the composition of the present invention. Thus, a ferrous salt may be used with one or more of the above recited class of metal salts. Of these, ferrous sulfate is particularly preferred. Among the other salts contemplated for use here are calcium ascorbate, calcium chloride, calcium iodate, calcium permanganate, calcium phosphate (mono-, di, and tribasic), calcium gluconate, zinc acetate, zinc carbonate, zinc chloride, zinc citrate, zinc iodate, zinc oxide, zinc permanganate, zinc peroxide, zinc salicylate, zinc stearate, zinc sulfate, magnesium chloride, magnesium citrate, magnesium chloride, magnesium sulfate, manganese chloride and copper sulfate. Preferred silver salts are silver nitrate, silver citrate, silver iodide and silver lactate. Iodine, in elemental form, and complexed with starch hydrolysate through heating and as iodine tincture, iodine salts, such as lugol solution, may also be added. Sodium and potassium iodide, sodium potassium iodate, calcium iodate and calcium iodide are particularly preferred. Dilute PVP-iodine solutions in water, normal saline on balanced salts solution may also be effectively employed in conjunction with the present treatment.

A further additional ingredient may be one or more of the adenosine phosphates, i.e., ATP, ADP or AMP.

In still yet another preferred embodiment of the composition of the present invention the composition includes a compound selected from the group consisting of alpha-ketoglutaric acid and pharmaceutically acceptable salts of alphaketoglutaric acid. Alpha-ketoglutaric acid and its salts accelerate collagen formation thus increasing the rate of healing of the wound to which the composition of the present invention is applied. This component is generally present in an amount of no more than 1-2%.

Finally, yet another component may be included in the composition of the present invention. This component is one or more amino acids which also improve healing. In a preferred embodiment one or more, up to all, of the following amino acids may be provided in the composition of the present invention: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, tyrosine, alanine, arginine, glycine, proline, histidine, serine, asparagine, aspartic acid, cysteine, cystine, glutamine and glutamic acid. Of these, glycine, proline and lysine are particularly preferred.

It will be understood that, as used herein, the term "amino acid" refers to both the pure form and the hydrochloric acid salts of the amino acids. Thus, in preferred embodiments of the present invention wherein amino acid is employed, one, two or all three of the above preferred amino acids are included in the composition of this invention. In general, the amount of amino acid in the composition should not exceed 1%.

In a particularly preferred embodiment, the composition of the instant invention includes starch hydrolysate and a monosaccharide selected from the group consisting of d-fructose, d-glucose, and d-sorbose. More preferably, the composition of the present invention comprises a starch hydrolysate having a dextrose equivalent of not more than 40, and d-fructose. Preferably, the fructose comprises up to about 30% of the total weight of the composition.

In other preferred embodiments, the composition comprising d-fructose and a starch hydrolysate having a dextrose equivalent of no more than 40 is supplemented with one or more of the following additives: an amino acid which is preferably one or more of the amino acids recited above; alpha-ketoglutaric acid or a pharmaceutically acceptable salt thereof; a ferrous salt, preferably ferrous sulfate; another pharmaceutically acceptable salt of a metal selected from the group consisting of calcium, zinc, manganese, magnesium, copper, selenium and silver.

In a particularly preferred embodiment of the present invention all of the above components are included in the composition. That is, a particularly preferred embodiment of the present invention is provided in a composition incorporating a principal amount of starch hydrolysate, having a dextrose equivalent between 13 and 17; d-fructose, present in a concentration of from 5 to 30 percent; ascorbic acid, present in the concentration of 1 to 5 percent; ferrous sulfate, present in a concentration of 0.1 to 1 percent; a zinc salt, present in a concentration of up to 1 percent; alphaketoglutarate present in a concentration of about 1-2% and at least one amino acid present in a concentration of 0.1 to 1 percent, all said percentages being by weight, based on the total weight of the composition.

In a wound which is only moderately infected or not yet infected, the inclusion of the monosaccharide is sufficient to control infection to acceptable levels. In the cases of particularly heavy infections, however, it may be desirable to also include, in small amounts one of the known antibiotics or antifungal agents commonly used in wound treatment. Among the useful antibiotics are streptomycin, penicillin, tetracycline, silver sulfadiazine, sulfanilamide, methylated sulfanilamide (sulfamylon®), cephalosporins, and amino-glycosides. Useful antifungal agents are nystatin, mycostatin®, or gramicidin. It must be noted that only small amounts of the antibiotic need be added.

The compositions of the present invention may be effectively employed in a regular program of wound treatment. For example, in the preferred method of wound treatment, a starch hydrolysate monosaccharide powder preparation is applied directly to the wound once or twice a day. Typically, the wound is first surgically debrided to remove all necrotic tissue. It is also possible to use water pulsating instruments to facilitate debridement; enzymatic debridement may prove useful as well, employing proteolytic enzymes such as Travase®, Biozyme®, collagenase or elase.

In accordance with the teachings of U.S. Patent No. 4,414,202, the wound is preferably irrigated, prior to application of the film forming composition, with a buffered salt solution having a pH between 6-7.8. It has also been found that irrigation and/or soaking the wound with dilute (0.05-1%) PVP-iodine solutions for 5 to 30 minutes before the addition of the composition aids in enhancing the effect of the dry material on wound healing. The wound is then covered with the starch hydrolysate/monosaccharide composition in an amount

sufficient to allow formation of a film over the wound. The wound may then optionally be covered with a preferred non-adhesive dressing, which may be removed for the daily repeat of the treatment. This method of treatment is particularly applicable to mammalian skin wounds, and is most suitable for treatment of human wounds.

When the monosaccharides are used as an active agent in a pretreatment solution, it is often desirable to include small amounts of pharmaceutically acceptable zinc, calcium, ferrous, copper, manganese, magnesium salts and silver. These optional components are generally only used in an amount of between about .001% to about 5%, preferably about .01 to about .1% of the total solution. These salts are known to have a beneficiating effect in the process of wound healing. Among the salts contemplated for use here are calcium ascorbate, calcium chloride, calcium iodate, calcium permanganate, calcium phosphate (mono-, di, and tribasic), calcium gluconate, zinc acetate, zinc carbonate, zinc chloride, zinc citrate, zinc iodate, zinc oxide, zinc permanganate, zinc peroxide, zinc salicylate, zinc stearate, zinc sulfate, magnesium chloride, magnesium citrate, silver nitrate, silver iodide, silver lactate, magnesium chloride, magnesium sulfate, manganese chloride, copper sulfate, ferrous sulfate, ferrous chloride or ferrous gluconate. Also useful are iodine salts, such as potassium, sodium, or calcium iodide or iodate, as well as elemental iodine or PVP-iodine. These may be used alone or in combination with the solution or dry powder, but in general it is preferred that the total amount of these additional components not exceed 5% overall. Other possible additives are very small amounts of antibiotics such as sulfonilamide (Sulfamylon®) sulfadiazine, silver-sulfadiazine, zinc-sulfadiazine, penicillin, tetracycline, cephalosporins, aminoglycosides, clindamycin and antifungal agents such as mycostatin®, nystatin, or gramicidin.

It will be recognized by one skilled in the art that, with respect to the components in the solution and the dry powder, since these are to be used to prevent microbial infection, the material should be sterilized prior to application. Although the method of sterilization is not particularly restricted, it is recommended that irradiation not be the method of choice, because of the possible effect of radiation on the molecular structure of the monosaccharide, particularly in solution. Dry heat sterilization has proven particularly suitable for the purposes of the present invention.

This method of controlling microbial growth is suitable for use on any mammalian skin wound. However, the present method is particularly well suited for the treatment of human skin.

The process of the present invention will be better understood by references to the following non-limiting examples.

Example 1

The following illustrate Examples of wound healing compositions of the present invention. In each case, fructose was a chemically pure fructose made by Pfanstiehl Laboratories, Inc. (Waukegan, Il1.) M-150 refers to a starch hydrolysate having a dextrose equivalent of 13-17 (Maltrin®, Grain Processing Corporation, Muscatine, Ia.). The starch hydrolysate was sterilized by radiation prior to use.

I. M-150 95g
fructose 5g

II. M-150 70g
fructose 30g

III. M-150 88g
fructose 10g
ascorbic acid 2g

IV. M-150 72g
fructose 15g
sodium ascorbate 3g

V. M-150 81g
fructose 15g
ascorbic acid 3g
amino acids
(20 amino acids in equal proportions) 1g

VI. M-150 77g
fructose 20g
potassium ascorbate 2g
glycine .33g
lysine .33g
proline .34g

VII M-150 80g
fructose 18g
-ketoglutarate 1g
ferrous sulfate .1g
amino acid
(20 amino acids in equal proportions) .9g

Example 2

A. An 84-year-old white female was affected with progressive brain syndrome, Alzheimer's disease, malnutrition, cachexia and a non-healing decubitus ulcer of the left ischiatic region. The ulcer measured, at time of admission, 5.5 x 6 x 1.8 cms. There were large amounts of foul-smelling, necrotic, gangrenous tissue. Cultures taken from the wound indicated the presence of the following bacteria: Proteus mirabilis, Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa.

Initially thorough debridement of necrotic tissue was carried out, followed by intensive irrigation with TIS-U-SOL®, a balanced salts solution. The ulcerated area was then filled with M-150, a D-glucose polysaccharide (starch hydrolysate) with a dextrose equivalent of 13-17. Treatment thereafter consisted of twice daily irrigation with the salt solution, and application of the starch hydrolysate. The ulcer was covered each time with a non-adhesive dressing. After 3 weeks of treatment, the infection decreased and the ulcer decreased in size, but healing was progressing very slowly.

At this point, treatment was continued in the same fashion, but instead of the starch hydrolysate alone, a mixture of starch hydrolysate and fructose, in a ratio of 80:20, was used. An immediate clinical response was manifested by more highly vascularized granulation tissue formation, a faster filling in of the crater, a rapid decrease in the surface area of the ulcer, and a faster growth of the epithelium. Further the exudate normally present in the ulcer decreased significantly, and the presence of a more sturdy, better organized, more clinging film over the granulation tissue was noticed. Multiple strands of this film could be seen clinging to and binding several areas of the ulcer granulation tissue platform. By the end of 3 weeks (a total of six weeks) the ischiatic ulcer was completely healed.

B. A 67-year-old woman afflicted with multiple sclerosis of 12 years duration was completely paralyzed, and had developed severe, deep infected Stage IV pressure ulcers of both hips, the sacral area, and both ischiatic regions.

She was admitted to the wound healing unit and underwent the following treatment; twice daily irrigation with a balanced, buffered salt solution, and sprinkling of M-150 starch hydrolysate powder. Healing and infection control began on the first day of treatment; by the end of the third week, the ulcerated areas had healed about 20% of the initial size. At that point, the lesions on the right side were treated with a mixture of starch hydrolysate (73 parts), fructose (24 parts), ascorbic acid (2 parts) and a mixture of 20 amino acids in equal proportions (1 part). The left side lesions received the same treatment as before, and acted as controls. By the end of 8 weeks, the ulcers treated with the complex formulation were 90% healed, whereas the control areas were only 35% healed.

EXAMPLE 3

The following example demonstrates one of the antibacterial effects of monosaccharide sugars in vitro. Tissue samples of infected lesions were excised by dermal punch from the center of each wound; each sample had an average weight of about 0.7g. Tissue samples were dipped in 95% ethanol and flamed dry to remove surface contamination; the tissue was then ground on a sterile mortar and pestle, with 1.0ml of saline until finaly macerated. Serial ten-fold dilutions were performed in saline and smaples plated by pour plate technique. Quantitation was then performed at 24 hours for facultative anaerobic bacteria and 48 hours for anaerobically incubated plates, and results recorded as microorganisms per gram of tissue. Following identification and quantification, all microorganisms were transferred to ETHA slants (ETHA was prepared by addition of 1.5% agar (DIFCO Labs) to enriched Todd-Hewitt broth, (ETHB) containind Todd-Hewitt Broth (Baltimore Biological Laboratories), 0.5% yeast extract (BBL), 0.05% hemin (Eastman Kodak Co.) and 0.005% menadione (Sigma Chemical Co.). All microorganisms were grown for 24 hours in ETHB before inoculation to sugars.

The following sugars were used for comparative testing of their bacteriostatic effects: glucose, and fructose, (monosaccharides) and sucrose and lactose (disaccharides). Each sugar solution is prepared in 10ml tubes of ETHB to concentrations of 10, 20, 30, 50 or 70% (W/V) and then autoclaved. The pH was adjusted to about 7.4. A 0.1ml inoculation containing approximately 1×10^8 organisms was then placed on all tubes, giving a final concentration of 1×10^8 organism/ml. Tubes were incubated aerobically for falcultatives, and anaerobically in Gas Pak jars (BBL) for obligate anaerobes. It designated time periods, tubes were removed from incubation and optical density measured on a Column Hitachi 124.

Results for two trials are shown in Tables 1 and 2. Observation of these test results show that, overall, the monosaccharides have an unexpectedly much more potent effect on the prevention of bacterial growth than do the disaccharides, requiring a much lower percentage of sugar to achieve bacteriostasis.

Table 1. Percent sugar necessary[1] to reduce growth of bacteria by 50% after 24 h of incubation[2]

Microorganism	Glucose	Sucrose	Fructose	Lactose
Enterococcus	21.5	29	11.5	N.D.[3]
Staphylococcus aureus	13.6	26	8.3	15.6
Proteus mirabilis	13.6	18.6	9.3	14.3
Peptostreptococcus	11	28	6	8.3

[1]Values are the average of results obtained from at least two clinical ioslates of each microorganism.
[2]Bacteria were incubated under appropriate conditions as described in Material and Methods.
[3]N.D. = not done

Table 2. Percent sugar necessary[1] to reduce growth of bacteria by 90% after 24 h of incubation[2]

Microorganism	Glucose	Sucrose	Fructose	Lactose
Enterococcus	28.3	64	21.2	N.D.[3]
Staphylococcus aureus	20	74.3	19.6	47
Proteus mirabilis	28.3	46	34.3	40
Peptostreptococcus	80	62	33.3	26.3

[1]Values are the average results obtained from at least two clinical isolates of each microorganism.
[2]Bacteria were incubated under appropriate conditions as described in Materials and Methods.
[3]N.D. = not done

EXAMPLE 4

The following Example shows the effective treatment of wounds using a monosaccharide containing pretreatment solution:

A. The subject was a 90 year old woman affected with progressive organic brain disease, paralysis, contractures of the upper and lower extremities and a large, deep pressure ulcer (bed sore) on the right trochanteric area measuring 12cms X 8cms X 2cms. Her pressure ulcer was filled with large amounts of necrotic tissue and abundant purulent, foul smelling exudate. X-rays of the hip showed the presence of a metallic hip replacement prosthesis and osteomyelitis of the femoral bone.

The pressure ulcer was treated twice daily with irrigation with balanced salts solution and sprinkled with a starch hydrolysate powder with a Dextrose Equivalent (D.E.) of 17. The ulcer was debrided of necrotic tissue daily as needed. Even though the attendant foul odor decreased with the use of the starch hydrolysate alone, the production of purulent exudate continued as the patient developed fevers of 102-103°F. The femoral head prosthesis was removed surgically and the remaining cavity was thoroughly irrigated with the balanced salts solution. Portions of the femur and acetabulum were curetted.

The remaining wound was then treated twice daily by irrigation with balanced salts solution and sprinkled with chemically pure fructose powder (Pfanstiehl Laboratories, Muscatine, I.A.). The remaining infection subsided almost completely. The foul odor characteristic of this infection subsided within 24-28 hours and healthy, highly vascularized granulation tissue began to fill the wound cavity. The epidermis as well began to grow in a centripetal manner. By the end of the 4th post-operative week the original ulcer site had healed 80% and the patient was discharged to an extended care facility.

B. A 72 year-old female suffered a subdural hematoma on the left occipital region; following a craniotomy, the subdural hematoma was removed. During the recovery period throughout which she was laid on her back, without being turned for several days, she developed a deep, severely infected, foul-smelling sacral pressure ulcer, State IV, which extended down to the sacral bone. She was treated initially with povidone-iodine soaks, which only had the effect of causing deterioration and enlargement of the ulcer.

At this point, treatment was initiated with a high fructose corn syrup powder (DE 42-55). The powder was sprinkled on the wound twice daily, following irrigation with a balanced salt solution. The infection came under control almost immediately by the second post-treatment day; this was also accompanied by formation of a highly vascularized fast growing granulation tissue.

Once the healing was initiated in this manner, a follow-up treatment was begun, approximately, 2 weeks after the HFGS treatment was started. Because the HFCS alone cannot form an adequate film to provide a barrier over the wound, a mixture of starch hydrolysate powder (DE-13-17) and HFCS powder (70:30) was prepared. The healing progressed rapidly until complete closure of the original ulcer was accomplished by the end of the 8th week.

Claims

1. A composition comprising at least one pharmaceutically acceptable monosaccharide containing from about 3 to 7 carbon atoms and a pharmaceutically acceptable film forming agent.

2. The composition of Claim 1 wherein said pharmaceutically acceptable film-forming agent is selected from the group consisting of starch hydrolysate having a dextrose equivalent of not more than 85, polyvinyl pyrollidone, polyvinyl alcohol, ethylene glycol, albumin, cellulose, gelatin, solubilized keratin, alginate, karaya gum, gum arabic, gum tragacanth, agar and locust bean gum, and the monosaccharide is selected from the group consisting of pharmaceutically acceptable ketose sugars and pharmaceutically acceptable aldose sugars.

3. A composition of Claims 1 or 2 wherein the film-forming agent is a starch hydrolysate having a dextrose equivalent of between about 5 and 40.

4. The composition of Claims 1-3 wherein said dextrose equivalent of said starch hydrolysate is in the range of between about 10 and 20, preferably, between about 13 and 17.

5. The composition of any one of Claims 1-4 wherein the monosaccharide is present in an amount from between .01 to about 50% by weight of the composition, preferably between about 5 to about 30%.

6. The composition of any one of Claims 1-5 wherein the pharmaceutically acceptable sugar is selected from the group consisting of erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, tylose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, and sedoheptulose.

7. The composition of any one of Claims 1-6 wherein the sugar is the D-isomer.

8. The composition of any one of Claims 1-7 wherein said sugar is fructose, glucose or sorbose.

9. The composition of any one of Claims 1-8 wherein the sugar is fructose.

10. The composition of any one of Claims 1-9 which comprises one or more additional compounds selected from the group consisting of ascorbic acid and pharmaceutically acceptable salts thereof, alpha ketoglutaric acid and pharmaceutically acceptable salts thereof, an amino acid, a pharmaceutically acceptable metal salt, and an iodine compound.

11. The composition of any one of Claims 1-10 which comprises a ferrous salt.

12. The composition of Claim 10 or 11 which comprises fructose in a concentration of 5 to 30%, ascorbic acid in a concentration of 1 to 5%, ferrous sulfate in a concentration of .01 - 1%, zinc salt in a concentration of 0.01- .1%, all said percents being by weight based on the total weight of the composition.

13. The use of a pharmaceutically acceptable monosaccharide having from 3 to 7 carbon atoms in controlling microbial growth in the wound of a mammal.

14. The use of Claim 13 wherein the monosaccharide is fructose.